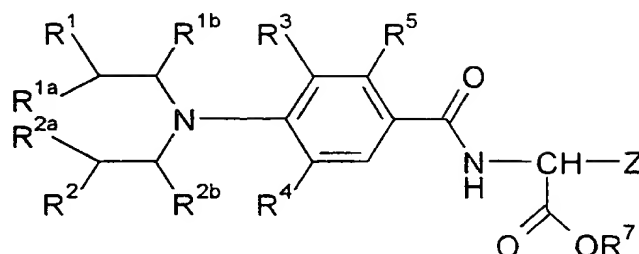


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CLAIMS

1. A compound of Formula I:



wherein:

5 R^1 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

R^2 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C₁₋₄ alkyl group, -F, -Cl, -Br, -I, -CN, or -NO₂;

R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

15 R^3 is -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃, -CF₃, -SF₅, -SCF₃, or -CF₂CF₃ ;

R^4 is -H, -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃, -CF₃, -SF₅, -SCF₃, or -CF₂CF₃ ;

20 R^5 is -H or -F;

with the proviso that if R^4 is -H, then R^3 is not -F;

R^7 is -H, -C(CH₃)₃, or -CH₂-CH=CH₂ ;

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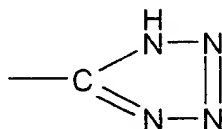
Z is $-\text{CH}_2-\text{T}-\text{W}$;

T is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, or $-(\text{SO}_2)-$;

the group $-\text{CH}_2-\text{T}-$ may optionally be substituted with 1 or 2 substituents, denoted Q^1 and Q^2 respectively, on carbon, wherein Q^1 and Q^2 are independently a C_{1-4} alkyl group or a halogen; or, when Q^1 and Q^2 are bonded to adjacent carbon atoms, Q^1 and Q^2 together may form a C_{3-4} alkylene radical optionally substituted with 1, 2, 3 or 4 substituents independently selected from C_{1-4} alkyl groups and halogens;

W is one of:

- (1) $-\text{COOH}$;
- (2) $-(\text{C}=\text{O})\text{OR}^8$;
- (3) $-(\text{C}=\text{O})\text{NR}^9\text{R}^9$;
- (4) $-\text{SO}_2\text{NHR}^{10}$;
- (5) $-\text{SO}_2\text{OR}^{11}$;
- (6) $-\text{PO}_3\text{R}^{11}\text{R}^{11}$;
- (7) a tetrazol-5-yl group:



- (8) $-\text{CONH}-\text{SO}_2\text{R}^{12}$; and,
- (9) $-\text{M}-\text{Het}$;

with the proviso that if T is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, or $-(\text{SO}_2)-$, then W is not $-\text{COOH}$;

wherein:

R^8 is a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{5-20} aryl group, or $-\text{CH}_2-\text{CH}=\text{CH}_2$;

wherein the C_{5-20} aryl group may optionally be substituted on carbon with from 1 to 4 substituents

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selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

R⁹ is independently -H, a C₁₋₆alkyl group, a C₃₋₆cycloalkyl group, a C₅₋₂₀aryl group, a C₇₋₉aralkyl group, or a C₅₋₂₀heteroaryl group linked to N via carbon;

wherein the C₅₋₂₀aryl group, the C₅₋₂₀heteroaryl group, and aryl moiety of the C₇₋₉aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

and wherein the C₃₋₆cycloalkyl group may optionally carry a methyl group;

R¹⁰ is a C₁₋₆alkyl group, -CH₂-CH=CH₂, a C₃₋₆cycloalkyl group, a C₁₋₄haloalkyl group (e.g., -CF₃, -CH₂CF₃), or a C₅₋₂₀aryl group;

wherein the C₅₋₂₀aryl group, the C₅₋₂₀heteroaryl group, and aryl moiety of the C₇₋₉aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

and wherein the C₃₋₆cycloalkyl group may optionally carry a methyl group;

R¹¹ represents -H, a C₁₋₆alkyl group, or a C₃₋₆cycloalkyl group;

R¹² is one of:

(a) a C₃₋₇cycloalkyl group;

(b) a C₁₋₆alkyl group, optionally substituted with one or more of: a phenyl group; a phenyl group with from 1 to 5 substituents selected from halogen, -NO₂, -CF₃, C₁₋₄alkyl, C₁₋₄alkoxy, -NH₂, -NHCOCH₃, -CONH₂, -OCH₂COOH, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂,

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-NHCOOC₁₋₄alkyl, -OH, -COOH, -CN and -COOC₁₋₄alkyl; a C₁₋₄alkyl group; a C₁₋₄haloalkyl group; or a halogen; and,

(c) a C₁₋₆perfluoroalkyl group;

5 M represents -S-, -SO-, or -SO₂- ; and,

Het represents a 5 or 6 membered heterocyclic aromatic ring linked to M via a carbon atom of the aromatic ring, said aromatic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of O, N and S said aromatic ring optionally being substituted on carbon
10 atoms of the ring with 1, 2, 3 or 4 substituents selected from the group consisting of -OH, -SH, -CN, -CF₃, NH₂ and halogen.

2. A compound according to claim 1, wherein:
15 R¹ and R² are independently -I, -Br, or -Cl.

3. A compound according to claim 1, wherein:
R¹ and R² are both -I.

4. A compound according to any one of claims 1 to 3, wherein:
20 R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or -CH₃.

5. A compound according to any one of claims 1 to 3, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.

6. A compound according to any one of claims 1 to 5, wherein:
25 R³ and R⁴ are -CF₃ and -H, respectively.

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7. A compound according to any one of claims 1 to 5,
wherein:
R³ and R⁴ are both -F.
- 5 8. A compound according to any one of claims 1 to 5,
wherein:
R³ and R⁴ are -CF₃ and -H, respectively; and,
R⁵ is -H.
- 10 9. A compound according to any one of claims 1 to 5,
wherein:
R³ and R⁴ are both -F; and,
R⁵ is -F.
- 15 10. A compound according to any one of claims 1 to 5,
wherein:
R³ and R⁴ are both -F; and,
R⁵ is -H.
11. A compound according to any one of claims 1 to 10,
wherein:
Z is -CH₂-T-C(=O)OH or -CH₂-T-C(=O)OR⁸ ; and,
T is -CH₂- .
- 20 12. A compound according to any one of claims 1 to 11,
wherein:
R⁸ is -H, -C(CH₃)₃, or -CH₂-CH=CH₂.
- 25 13. A compound selected from:
{3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-
glutamic acid; and,
the di-tert-butyl ester thereof.

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14. A compound selected from:
3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

5 15. A compound selected from:
{3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

10 16. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

15 17. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

20 18. A compound selected from:
{2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

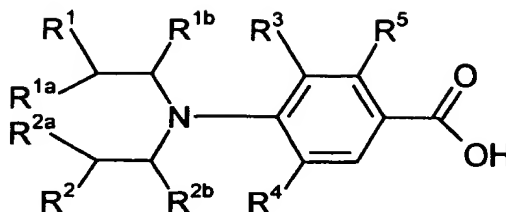
19. A compound selected from:
{3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

25 20. A compound selected from:
{3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

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21. A compound of Formula II:



wherein:

R^1 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

R^2 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C₁₋₄ alkyl group, -F, -Cl, -Br, -I, -CN, or -NO₂;

R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;

R^3 is -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃, -CF₃, -SF₅, -SCF₃, or -CF₂CF₃ ;

R^4 is -H, -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃, -CF₃, -SF₅, -SCF₃, or -CF₂CF₃ ;

R^5 is -H or -F;

with the proviso that if R^4 is -H, then R^3 is not -F;

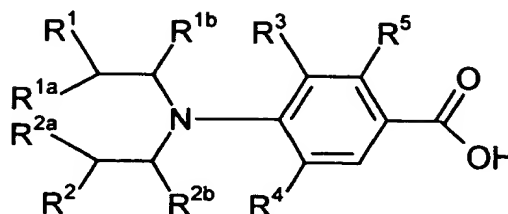
and,

with the proviso that if R^1 is -Cl, R^2 is -Cl, R^{1a} is -H, R^{2a} is -H, R^{1b} is -H, R^{2b} is -H, R^4 is -H, and R^5 is -H, then R^3 is not -CH₃.

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22. A compound of Formula II:



wherein:

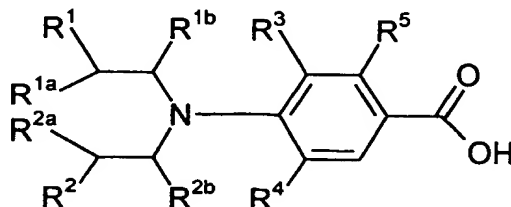
 R^1 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ; R^2 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C₁₋₄ alkyl group, -F, -Cl, -Br, -I, -CN, or -NO₂;

 R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
 R^3 is -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CF₃,
-SF₅, -SCF₃, or -CF₂CF₃ ;

 R^4 is -H, -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CF₃,
-SF₅, -SCF₃, or -CF₂CF₃ ;
 R^5 is -H or -F;with the proviso that if R^4 is -H, then R^3 is not -F.

23. A compound of Formula II:



wherein:

 R^1 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ; R^2 is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;

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wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C₁₋₄ alkyl group, -F, -Cl, -Br, -I, -CN, or -NO₂;
R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
R³ and R⁴ are -CF₃ and -H, respectively,
or R³ and R⁴ are both -F;
R⁵ is -H or -F.

24. A compound according to any one of claims 21 to 23, wherein:
R¹ and R² are independently -I, -Br, or -Cl.
25. A compound according to any one of claims 21 to 23, wherein:
R¹ and R² are both -I.
26. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or -CH₃.
27. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.
28. A compound according to any one of claims 21 to 27, wherein:
R³ and R⁴ are -CF₃ and -H, respectively.
29. A compound according to any one of claims 21 to 27, wherein:
R³ and R⁴ are both -F.

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30. A compound according to any one of claims 21 to 27,
wherein:
 R^3 and R^4 are $-CF_3$ and $-H$, respectively; and,
 R^5 is $-H$.
31. A compound according to any one of claims 21 to 27,
wherein:
 R^3 and R^4 are both $-F$; and,
 R^5 is $-F$.
32. A compound according to any one of claims 21 to 27,
wherein:
 R^3 and R^4 are both $-F$; and,
 R^5 is $-H$.
33. 3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoic acid.
34. 3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoic acid.
35. 3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoic acid.
36. 2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoic acid.
37. 2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoic acid.
38. 2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoic acid.
39. 3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoic acid.
40. 3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoic acid.

ART 34 AMEND

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41. A two-component system comprising:
- (i) a first component capable of delivering a carboxypeptidase enzyme to the interior or exterior of a target cell or a vector encoding said enzyme to the interior of said cell such that said vector expresses said enzyme in said cell, and
 - (ii) a prodrug of according to any one of claims 1 to 20 capable of being converted by said enzyme into a drug according to any one of claims 21 to 40.
42. A kit comprising:
- (a) a compound according to any one of claims 1 to 20; and,
 - (b) one of:
 - (i) an immunoglobulin/enzyme fusion protein or conjugate in which the immunoglobulin is specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;
 - (ii) a ligand/enzyme conjugate or fusion protein, the ligand being specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;
 - (iii) a vector which encodes a carboxypeptidase enzyme which can be expressed in a cell.
43. A composition comprising a compound according to any one of claims 1 to 40, and a pharmaceutically acceptable carrier or diluent.
44. A compound according to any one of claims 1 to 40 for use in a method of treatment of the human or animal body.

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45. A compound according to any one of claims 1 to 40 for use in a method of treatment of cancer of the human or animal body.
46. Use of a compound according to any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of cancer.
47. A method for the treatment of cancer comprising administering to a subject suffering from cancer a therapeutically-effective amount of a compound according to any one of claims 1 to 40.